



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460

OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

30/JAN/1998

MEMORANDUM

Subject: EPA Reg. No: 264-LTE  
DP Barcode: D 235987  
Case No: 061591

From: Masih Hashim, Toxicologist  
Technical Review Branch *M/H*  
Registration Division (7505C) *SCR*

To: Vickie Walters, PM Team 25  
Herbicide Branch  
Registration Division (7505C)

Applicant: Rhone-Poulenc AG Company  
2 T.W Alexander Drive  
Research Triangle Park, N.C. 27709

FORMULATION FROM LABEL:

<u>Active Ingredient(s):</u>	<u>% by wt.</u>
121601 Acetochlor (ANSI)	44.6
123000 Isoxaflutole	4.2
<u>Inert Ingredient(s):</u>	<u>51.2</u>
Total:	100%

**BACKGROUND:** Rhone-Poulenc Company has submitted a set of six acute toxicity studies in support of the registration for Balance Pro Herbicide. The MRID numbers are 442362-02 through 07. These tox studies (except sensitization) were reviewed by Dynamac Corporation and revised by TRB if deemed necessary. All tests were conducted at the Corning Hazleton Laboratories in Madison, WI.

**RECOMMENDATION:**

Each of the six studies is acceptable in accordance with the sub Division F guidelines. The acute toxicology profile for the File Symbol # 264-LTE is as follows:

acute oral toxicity	III	acceptable
acute dermal toxicity	III	acceptable
acute inhalation toxicity	IV	acceptable
primary eye irritation	III	acceptable
primary skin irritation	I	acceptable
dermal sensitization	sensitizer	acceptable

**LABELING:**

ID #: 000264-00572 BALANCE PRO HERBICIDE

**RESTRICTED USE CLASSIFICATION RECOMMENDED:**

Due to dermal irritation toxicity category.

The PM Team should decide if restricted use classification is necessary or if alternative labeling will allay the requirement for restricted use classification.

**SIGNAL WORD:** DANGER PELIGRO

**PRECAUTIONARY STATEMENTS:**

Corrosive. Causes skin burns. Harmful if swallowed or absorbed through skin. Causes moderate eye irritation. Do not get on skin or on clothing. Avoid contact with eyes. Wear coveralls over long-sleeved shirt and long pants, socks and chemical resistant footwear and chemical resistant gloves (such as Nitrile, Butyl, Neoprene, and/or Barrier Laminate). Prolonged or frequently repeated skin contact may cause allergic reaction in some individuals. Wash thoroughly with soap and water after handling. Remove contaminated clothing and wash clothing before reuse.

**STATEMENT OF PRACTICAL TREATMENT (SOPT):**

IF SWALLOWED: Call a physician or Poison Control Center. Do not induce vomiting. Drink promptly a large quantity of milk, egg whites, gelatin solution, or if these are not available, drink large quantities of water. Avoid alcohol.

IF ON SKIN: Wash with plenty of soap and water. Get medical attention. For Category III, add "if symptoms persist."

IF IN EYES: Flush eyes with plenty of water. Call a physician if irritation persists.

#### NOTE TO PHYSICIAN:

The proposed label should contain a Note to Physicians. Some suggested types of information include the following:

- technical information on symptomatology;
- use of supportive treatments to maintain life functions;
- medicine that will counteract the specific physiological effects of the pesticide;
- company telephone number to specific medical personnel who can provide specialized medical advice.

#### NOTE TO PHYSICIAN (Cont.):

Probable mucosal damage may contraindicate the use of gastric lavage.

## ACUTE TOX ONE-LINER

1. PC CODE: 121601, 123000

2. CURRENT DATE: 1-30-98

3. TEST MATERIAL:

121601 Acetochlor (ANSI)

44.6%

123000 Isoxaflutole

4.2%

Study/Species/Lab/ Project Identification/Date	MRID Number	Results	Tox. Cat.	Core Grade
acute oral toxicity/rat/Corning Hazleton/CHW 60904131/ 2-21-97	442362-02	LD <sub>50</sub> = 2599 mg/kg	III	A
acute dermal toxicity /rabbit /Corning Hazleton/CHW 60904132 / 1-30-97	442362-03	LD <sub>50</sub> >2000 mg/kg	III	A
acute inhalation /rat/Corning Hazleton/1160/1-1050 /1-7-97	442362-04	LC <sub>50</sub> >2.79 mg/L	IV	A
primary eye irritation /rabbit /Corning Hazleton / CHW 60904134 /1-30-97	442362-05	moderate ocular irritant	III	A
primary dermal irritation / Corning Hazleton / CHW 60904133 / 1-30-97	442362-06	severely irritating	I	A
dermal sensitization/ Corning Hazleton /CHW 60904135 /2- 20-97	442362-07	sensitizer	-	A

Core Grade Key: A = Acceptable, S = Supplementary (upgradable )

U = Unacceptable, V = Self Validated

## DATA REVIEW FOR DERMAL SENSITIZATION TESTING (§81-6, 870-2500)

Product Manager: 25  
MRID No: 442362-07

Reviewer: Masih Hashim  
Study Completion Date: 2-20-97  
Study No. CHW 60904235

Testing Facility: Corning Hazleton  
Author(s): S M Glaza  
Quality Assurance (40 CFR §160.12): Included

Test Material: Balance Pro Herbicide  
Positive Control Material: 2,4-dinitrochlorobenzene

Species: guinea pig/(HA)BR  
Weight: 350-550 g                      Age: young adult  
Source: Charles River  
Method: Buehler

### Summary:

1. This product is a dermal sensitizer.
2. Classification: acceptable

Procedure (Deviation From §81-6): none

Procedure: 0.4 ml of the undiluted test substance was topically applied each week to 20 guinea pigs during the induction period for three weeks. The challenge dose (undiluted) was applied two weeks following the induction period.

Ten guinea pigs were treated with the positive control diluted with 0.1% w/v in 80% ethanol for induction, and 0.05% mixture in acetone for the challenge. Test and positive control animals were evaluated at 24 and 48 hrs after each application.

All animals were graded and scored at 24 and 48 hours after each application.

### Results:

Positive erythema reaction was seen in all test animals at the challenge phase. The test substance is a sensitizer.

No reaction was seen in any of the ten naive control animals.

Strong erythema reactions were seen in all ten positive control animals at the challenge phase.

# DATA EVALUATION RECORD

EXP-31498A  
(Acetochlor and Isoxaflutole)

Study Type: Acute Six Pack (81-1 through -5)

Work Assignment No. 3-14 (D235987)

Prepared for

Registration Division  
Office of Pesticide Programs  
U.S. Environmental Protection Agency  
1921 Jefferson Davis Highway  
Crystal Mall II  
Arlington, VA 22202

Prepared by

Pesticide Health Effects Group  
Sciences Division  
Dynamac Corporation  
2275 Research Boulevard  
Rockville, MD 20850-3268

Primary Reviewer:  
Christie E. Padova, B.S.

Signature: Christie E. Padova  
Date: 8-8-97

Project Manager:  
Mary Menetrez, Ph.D.

Signature: Mary L Menetrez  
Date: 8/21/97

## Disclaimer

This Data Evaluation Record may have been altered by the Registration Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: Masih Hashim  
Review Section, Technical Review Branch (7505C)

MA

DATA EVALUATION RECORD
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STUDY TYPE: Acute Oral Toxicity - Rat

OPPTS Number: 870.1100

OPP Guideline Number: §81-1

DP BARCODE: D235987

SUBMISSION CODE: S523853

P.C. CODE: 121601 and 123000

TOX. CHEM. NO.:

EPA REG. NO.: 264-LTE

TEST MATERIAL (PURITY): EXP-31498A [44.6% (w:w) acetochlor and 4.2% (w:w) isoxaflutole]

SYNONYMS: Balance Pro Herbicide; RPA201772 (isoxaflutole); 4-(2-methanesulfonyl-4-trifluoromethylbenzoyl)-5-cyclopropyl isoxazole (isoxaflutole); 2-chloro-N-(ethoxymethyl)-N-(2-ethyl-6-methylphenyl) acetamide (acetochlor)

CITATION: Glaza, S. (1997) Acute oral toxicity study of EXP-31498A in rats. Corning Hazleton, Inc., Madison, WI. Laboratory Project Identification CHW 60904131. February 21, 1997. MRID 44236202. Unpublished.

SPONSOR: Rhone-Poulenc Ag Company, P.O. Box 12014, 2 T.W. Alexander Drive, Research Triangle Park, NC.

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 44236202), groups of five young adult Crl:CD(SD)BR albino rats/sex were given single oral doses of EXP-31498A [44.6% (w:w) acetochlor and 4.2% (w:w) isoxaflutole] at 1,000, 2,000 or 5,000 mg/kg (limit dose). The test substance was administered as received, and the animals were observed for clinical signs of toxicity and mortality for up to 14 days postdosing.

Oral LD<sub>50</sub> Males = 2,820 (1,670-4,761) mg/kg (95% C.I.)  
Females = 2,330 (1,257-4,318) mg/kg  
Combined = 2,599 (1,723-3,919) mg/kg

EXP-31498A is classified as **TOXICITY CATEGORY III** based on the calculated LD<sub>50</sub> values for both sexes.

Mortality occurred in 13/20 animals tested at ≥2,000 mg/kg, generally on day 1. Clinical effects observed in both decedent and surviving animals included staggered gaits, hypoactivity, and red-stained faces. Additional effects observed only in decedent animals included dyspnea, prostration, excessive salivation, hypothermic to touch, yellow- or tan-stained urogenital area, tremors, thin appearance, absence of righting reflex, and lacrimation. Effects generally subsided from surviving animals

by day 3. No treatment-related effect on body weight was observed in surviving animals, and necropsy after 14 days revealed no treatment-related abnormalities. Necropsy of decedent animals revealed abnormal contents of the gastrointestinal tracts in 7/13 animals and multiple dark red foci on all lobes of the liver in a single female from the 5,000-mg/kg dose group.

This study is classified **acceptable** (§81-1) and satisfies the guideline requirement for an acute oral study in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

## I. MATERIALS AND METHODS

### A. MATERIALS:

1. Test Material: EXP-31498A  
Description: Clear, light-brown liquid  
Reference #: 218-DAL-95  
Purity: 44.6% (w:w) Acetochlor and 4.2% (w:w) isoxaflutole  
Bulk density: 1.07 g/mL (temperature not specified)  
CAS #: 34256-82-1 and 141112-29-0, respectively
2. Vehicle: None employed
3. Test animals: Species: Rat  
Strain: Crl:CD(SD)BR, albino  
Age: Young adult (6-12 weeks)  
Weight: 240-299 g males; 210-251 g females  
Source: Charles River Laboratories, Portage, MI or Kingston, NY  
Acclimation period: ≥7 Days  
Diet: Purina Laboratory Rodent Diet (#5001), ad libitum  
Water: Tap water, ad libitum  
Housing: Group-housed, separated by sex

### B. STUDY DESIGN and METHODS:

1. In-life dates: October 23-November 22, 1996
2. Animal assignment and treatment: Animals were assigned to the test groups noted in Table 1. Following a 17- to 20-hour fasting period, rats were given a single oral dose of neat EXP-31498A by gavage. The rats were observed for signs of gross toxicity and/or mortality at approximately 1, 2.5,

and 4 hours postdosing, and at least once daily thereafter for the remainder of the 14-day study; body weights were recorded at 0 (prior to dosing), 7, and 14 days. At 14 days, the surviving animals were sacrificed, and all animals (upon death) were necropsied and examined for gross pathological changes.

TABLE 1. Doses, mortality/animals treated

Dose, mg/kg	Males	Females	Combined
1,000	0/5	0/5	0/10
2,000	1/5	2/5	3/10
5,000 <sup>a</sup>	5/5	5/5	10/10

<sup>a</sup>Limit dose

3. Statistics: The acute oral LD<sub>50</sub> values (with 95% C.I.) were calculated on a computer using a modified Behren-Reed-Muench cumulant method [Thakur, A., and W. Fezio. Drug and Chemical Toxicology, 4(3): 297-305 (1981)].

## II. RESULTS AND DISCUSSION:

- A. Mortality: Mortality data are presented in Table 1. Mortality (either as spontaneous death or animals sacrificed in extremis) occurred in 13/20 animals tested at  $\geq 2,000$  mg/kg; 12/13 animals died on day 1 and a single male from the 5,000-mg/kg dose group died on day 5.

Oral LD<sub>50</sub> Males = 2,820 (1,670-4,761) mg/kg (95% C.I.)  
Females = 2,330 (1,257-4,318) mg/kg  
Combined = 2,599 (1,723-3,919) mg/kg

- B. Clinical observations: Clinical effects observed in decedent animals included staggered gait (13/13), hypoactivity (12/13), dyspnea (6/13), prostration (5/13), red-stained face (2/13), excessive salivation (2/13), hypothermic to touch (2/13), yellow- or tan-stained urogenital area (2/13), tremors (1/13), thin appearance (1/13), absence of righting reflex (1/13), and lacrimation (1/13). Effects observed in surviving animals included red-stained face (5/17), staggered gait (4/17), hypoactivity (3/17), and alopecia of the dorsal area (1/17). Aside from alopecia, which was observed between 3 and 14 days, effects subsided from surviving animals by day 3.

- C. Body Weight: No treatment-related effect on body weight was observed in surviving animals. Overall (0-14 days), males gained averages of 42-44% and females gained averages of 20-24%.
- D. Necropsy: Gross necropsy of decedent animals revealed abnormal contents of the gastrointestinal tracts in 7/13 animals and multiple dark red foci on all lobes of the liver in a single female from the 5,000-mg/kg dose group. Necropsy of animals sacrificed after 14 days revealed no visible lesions.
- E. Deficiencies: There were no deficiencies that affected the validity of the study results.

EPA Reviewer: Masih Hashim  
Review Section, Technical Review Branch (7505C)

MH

DATA EVALUATION RECORD
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STUDY TYPE: Acute Dermal Toxicity - Rabbit

OPPTS Number: 870.1200

OPP Guideline Number: S81-2

DP BARCODE: D235987

SUBMISSION CODE: S523853

P.C. CODE: 121601 and 123000

TOX. CHEM. NO.:

EPA REG. NO.: 264-LTE

TEST MATERIAL (PURITY): EXP-31498A [44.6% (w:w) acetochlor and 4.2% (w:w) isoxaflutole]

SYNONYMS: Balance Pro Herbicide; RPA201772 (isoxaflutole); 4-(2-methanesulfonyl-4-trifluoromethylbenzoyl)-5-cyclopropyl isoxazole (isoxaflutole); 2-chloro-N-(ethoxymethyl)-N-(2-ethyl-6-methylphenyl) acetamide (acetochlor)

CITATION: Glaza, S. (1997) Acute dermal toxicity study of EXP-31498A in rabbits. Corning Hazleton, Inc., Madison, WI. Laboratory Project Identification CHW 60904132. January 30, 1997. MRID 44236203. Unpublished.

SPONSOR: Rhone-Poulenc Ag Company, P.O. Box 12014, 2 T.W. Alexander Drive, Research Triangle Park, NC.

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 44236203), five young adult New Zealand White rabbits/sex were dermally exposed to EXP-31498A [44.6% (w:w) acetochlor and 4.2% (w:w) isoxaflutole] at 2,000 mg/kg (limit dose) for 24 hours. The test substance was applied as received to approximately 10% of the total body surface area. Animals were observed for clinical signs of toxicity and mortality for up to 14 days postdosing.

**Dermal LD<sub>50</sub> Males = >2,000 mg/kg (observed)**

**Females = >2,000 mg/kg (observed)**

EXP-31498A is classified as **TOXICITY CATEGORY III** based on the observed LD<sub>50</sub> values for both sexes.

All animals survived the 14-day observation period. A decrease in food consumption was observed in a single male on day 3 and a decreased use of high limbs was observed in a single female between days 6 and 14. Severe dermal irritation, characterized by erythema, edema, blanching, atonia, coriaceousness, fissuring, necrosis, and desquamation, was observed at all test sites throughout the 14-day observation period. The body weights of 1/5 males and 2/5 females decreased between 0 and 7 days. All

animals then gained weight between 7 and 14 days; however, a single female exhibited an overall decrease of 6.6%. Aside from treatment-site dermal abnormalities, gross necropsy of animals sacrificed after 14 days revealed no visible lesions.

This study is classified **acceptable** (§81-2) and satisfies the guideline requirement for an acute dermal study in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

## I. MATERIALS AND METHODS

### A. MATERIALS:

1. Test Material: EXP-31498A  
Description: Clear, light-brown liquid  
Reference #: 218-DAL-95  
Purity: 44.6% (w:w) Acetochlor and 4.2% (w:w) isoxaflutole  
Bulk density: 1.07 g/mL (temperature not specified)  
CAS #: 34256-82-1 and 141112-29-0, respectively
2. Vehicle: None employed
3. Test animals: Species: Rabbit  
Strain: Hra: (NZW)SPF  
Age: Young adult (approximately 14 weeks)  
Weight: 2.160-2.503 kg (combined sexes)  
Source: HRP, Inc., Kalamazoo, MI  
Acclimation period: >7 Days  
Diet: Purina Laboratory Rabbit Diet HF (#5326), unspecified measured amount/animal/day  
Water: Tap water, ad libitum

### B. STUDY DESIGN and METHODS:

1. In-life dates: October 17-31, 1996
2. Animal assignment and treatment: Fur from the dorsal trunk areas (approximately 20% of the total body surface area) of each animal was clipped 1 day prior to dermal administration of EXP-31498A at 2,000 mg/kg (limit dose). The test material was evenly applied as received to approximately 180 cm<sup>2</sup>, equivalent to approximately 10% of the total body surface area. Each test site was covered with a 4-ply 9.5- x 19-cm gauze patch secured with paper tape, and the torso of each animal was wrapped with Saran Wrap secured with Elastoplast tape. In

addition, each animal was fitted with a restraining collar. After 24 hours, the coverings and collars were removed, and each application site was washed with tap water and dried with paper towels. The rabbits were observed for signs of gross toxicity and/or mortality at 1, 2.5, and 4 hours following treatment, and at least once daily thereafter for up to 14 days. Dermal irritation was graded using the Draize scale on days 1 (30 minutes following patch removal), 3, 7, 10, and 14. Body weights were recorded at 0 (prior to dosing), 7, and 14 days. At 14 days, the surviving animals were sacrificed, necropsied, and examined for gross pathological changes.

3. Statistics: Not applicable to this study.

## II. RESULTS AND DISCUSSION:

- A. Mortality: All animals survived the 14-day observation period.

Dermal LD<sub>50</sub> Males = >2,000 mg/kg (observed)  
Females = >2,000 mg/kg (observed)

- B. Clinical observations: A decrease in food consumption was observed in a single male on day 3 and a decreased use of high limbs was observed in a single female between days 6 and 14. No other effects were observed during the 14-day study.

Moderate to severe erythema (scores of 2-3; mean of 2.52) and slight to severe edema (scores of 1-3; mean of 2.24) were observed at all test sites during the 14-day study. All sites also exhibited blanching between 1 and 3 days, slight to moderate atonia between 1 and 14 days, slight to moderate coriaceousness and fissuring between 3 and 14 days, possible necrotic areas between 7 and 14 days, and slight desquamation between 10 and 14 days. Subcutaneous hemorrhaging was also observed at 1/6 sites at 3 days, denuded areas were observed at 2/6 sites at 14 days, and possible scar tissue was observed at 3/6 sites at 14 days.

- C. Body Weight: The body weights of 1/5 males and 2/5 females decreased between 0 and 7 days. All animals then gained weight between 7 and 14 days; however, a single female exhibited an overall (0-14 days) decrease of 6.6%. The remaining animals exhibited overall increases, ranging from 0.80 to 9.0% in males and 2.1 to

5.1% in females.

- D. Necropsy: Aside from treatment-site dermal abnormalities, gross necropsy of animals sacrificed after 14 days revealed no visible lesions.
- E. Deficiencies: There were no deficiencies that affected the validity of the study results.

EPA Reviewer: Masih Hashim  
Review Section: Technical Review Branch (7505C)

DATA EVALUATION RECORD
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STUDY TYPE: Acute Inhalation Toxicity - Rat

OPPTS Number: 870.1300

OPP Guideline Number: S81-3

DP BARCODE: D235987

SUBMISSION CODE: S523853

P.C. CODE: 121601 and 123000

TOX. CHEM. NO.:

EPA REG. NO.: 264-LTE

TEST MATERIAL (PURITY): EXP-31498A [44.6% (w:w) acetochlor and 4.2% (w:w) isoxaflutole]

SYNONYMS: Balance Pro Herbicide; RPA201772 (isoxaflutole); 4-(2-methanesulfonyl-4-trifluoromethylbenzoyl)-5-cyclopropyl isoxazole (isoxaflutole); 2-chloro-N-(ethoxymethyl)-N-(2-ethyl-6-methylphenyl) acetamide (acetochlor)

CITATION: Mould, A. (1997) EXP-31498A: Single dose inhalation (nose-only) toxicity study in the rat. Corning Hazleton (Europe), North Yorkshire, England. Laboratory Project Identification CHE 1160/1-1050. January 1997. MRID 44236204. Unpublished.

SPONSOR: Rhone-Poulenc Ag Company, P.O. Box 12014, 2 T.W. Alexander Drive, Research Triangle Park, NC.

EXECUTIVE SUMMARY: In an acute inhalation toxicity study (MRID 44109913), five young adult Crl:CDBR albino rats/sex were exposed by nose-only inhalation to EXP-31498A [44.6% (w:w) acetochlor and 4.2% (w:w) isoxaflutole] at 2.79 mg/L (>limit concentration) for 4 hours. Animals were observed for clinical signs of toxicity and mortality for up to 14 days postexposure.

Inhalation LC<sub>50</sub> Males = >2.79 mg/L (observed)  
Females = >2.79 mg/L (observed)

EXP-31498A is classified as **TOXICITY CATEGORY IV** based on the observed LC<sub>50</sub> values in both sexes.

All animals survived the 14-day observation period. Effects were observed for up to 1 day following exposure and included lethargy, coldness to the touch, labored respiration, ataxia, wet fur, stained fur, chromodacryorrhea, and nasal discharge. No significant effect on body weight was observed. Necropsy revealed enlarged mandibular lymph nodes (5/10) and dark areas of lungs (2/10).

This study is classified **acceptable** (S81-3) and satisfies the guideline requirement for an acute inhalation study in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

## I. MATERIALS AND METHODS

### A. MATERIALS:

1. Test Material: EXP-31498A  
Description: Clear, light-brown liquid  
Reference #: 218-DAL-95  
Purity: 44.6% (w:w) Acetochlor and 4.2% (w:w) isoxaflutole  
Bulk density: 1.07 g/mL (temperature not specified)  
CAS #: 34256-82-1 and 141112-29-0, respectively
2. Vehicle and/or positive control: None employed
3. Test animals: Species: Rat  
Strain: Crl:CDBR  
Age: Young adult (approximately 10 weeks)  
Weight: 293-397 g males; 201-275 g females  
Source: Charles River UK Limited, Margate, Kent, UK  
Acclimation period: ≥5 Days  
Diet: SQC Rat and Mouse Maintenance Diet No. 1, Expanded (Special Diet Services, UK), ad libitum, except during exposure  
Water: Mains drinking water, ad libitum, except during exposure  
Housing: Two-three/cage, separated by sex

### B. STUDY DESIGN and METHODS:

1. In-life dates: November 8-22, 1996
2. Exposure conditions: A cylindrical continuous-flow 40-L exposure chamber constructed of aluminum was used. The chamber was equipped with radial ports for attachment of individual animal restraining cones for nose-only exposure.

To generate test atmosphere, the test material was metered using a peristaltic pump to a Sachsse liquid nebulizer located immediately above the exposure chamber; the nebulizer was operated with compressed breathing-quality air. The resultant aerosol was diluted with additional air prior to entering the exposure chamber. Airflow through the chamber was maintained at 30 L/min (equivalent to 45 chamber turnovers/hour). The time required for equilibration of the chamber was not provided;

however, it was evident from the first chamber concentration determination (0.82 mg/L) that equilibrium had not been reached at 30 minutes.

The nominal test atmosphere concentration was calculated at the end of the exposure period by dividing the total amount of test material delivered to the chamber by the total air volume passing through the chamber during the exposure time. The actual test atmosphere concentration was determined gravimetrically twice/hour during exposure. Atmospheric samples were drawn for 2 minutes through open-face glass fiber filters located at a representative breathing zone site. Dry weights were obtained, and the actual concentration was then back-calculated by dividing by the percent of solids in the test material (57.1%). The nominal and average gravimetrically-determined test concentrations were 11.1 and 2.79 mg/L, respectively.

Particle size was determined once/hour during exposure using an Andersen 298 Marple Cascade Impactor. Samples were drawn for 2 minutes from a representative breathing zone site. The calculated mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) averaged 1.64 and 1.91  $\mu\text{m}$ , respectively.

The temperature, relative humidity, and oxygen level were recorded every 30 minutes during exposure and averaged 21 °C, 68%, and 20.7%, respectively.

3. Animal assignment and treatment: Five young adult rats/sex were exposed to EXP-31498A at 2.79 mg/L via nose-only inhalation for 4 hours. The animals were observed for signs of toxicity and/or mortality at hourly intervals during both the exposure period and the remainder of the exposure day, and at least once daily thereafter for the remainder of the 14-day study. Body weights were recorded on days 0 (prior to exposure), 1, 7, and 14. After 14 days, the surviving animals were sacrificed, necropsied, and examined for gross pathological changes.
4. Statistics: Not applicable to this study.

## II. RESULTS AND DISCUSSION:

- A. Mortality: All animals survived the 4-hour exposure and 14-day observation periods.

Inhalation LC<sub>50</sub> Males = >2.79 mg/L (observed)

Females = >2.79 mg/L (observed)

- B. Clinical observations: Treatment-related effects were observed on day 0 and included lethargy (10/10), coldness to the touch (10/10), labored respiration (2/10), and ataxia (1/10). Additional effects that were attributed to the method of restraint included wet fur, stained fur, chromodacryorrhea, and nasal discharge. Effects subsided from all animals by day 2.
- C. Body Weight: Upon comparison of the 0-, 7-, and 14-day data, no significant effect on body weight was observed. Overall (0-14 days), all animals gained weight, with average increases of 17% for males and 9.0% for females.
- D. Necropsy: Gross necropsy of animals sacrificed after 14 days revealed enlarged mandibular lymph nodes (5/10) and dark areas of lungs (2/10).
- E. Deficiencies: There were no deficiencies that affected the validity of the study results.

EPA Reviewer: Masih Hashim

Review Section: Technical Review Branch (7505C)

## DATA EVALUATION RECORD

STUDY TYPE: Primary Eye Irritation - RabbitOPPTS Number: 870.2400OPP Guideline Number: S81-4DP BARCODE: D235987SUBMISSION CODE: S523853P.C. CODE: 121601 and 123000TOX. CHEM. NO.:EPA REG. NO.: 264-LTETEST MATERIAL (PURITY): EXP-31498A [44.6% (w:w) acetochlor and 4.2% (w:w) isoxaflutole]

SYNONYMS: Balance Pro Herbicide; RPA201772 (isoxaflutole); 4-(2-methanesulfonyl-4-trifluoromethylbenzoyl)-5-cyclopropyl isoxazole (isoxaflutole); 2-chloro-N-(ethoxymethyl)-N-(2-ethyl-6-methylphenyl) acetamide (acetochlor)

CITATION: Glaza, S. (1997) Primary eye irritation study with EXP-31498A in rabbits. Corning Hazleton Inc., Madison, WI. Laboratory Project Identification CHW 60904134. January 30, 1997. MRID 44236205. Unpublished.

SPONSOR: Rhone-Poulenc Ag Company, P.O. Box 12014, 2 T.W. Alexander Drive, Research Triangle Park, NC.

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 44236205), 0.1 mL of EXP-31498A [44.6% (w:w) acetochlor and 4.2% (w:w) isoxaflutole] was instilled into the conjunctival sac of the right eye of six young adult New Zealand White rabbits (five male and one female). The treated eyes were not rinsed. The animals were observed for up to 7 days following treatment, and eye irritation was scored using the Draize scheme.

Ocular irritation was greatest in the treated eyes 1 hour following instillation (maximum score of 34.8) and included scattered or diffuse corneal opacity affecting up to 100% of the total area, circumcorneal injection of the iris, moderate conjunctival redness, slight to moderate conjunctival chemosis, and severe clear conjunctival discharge in 6/6 treated eyes. Blanching was also observed in up to 6/6 treated eyes between 1 and 48 hours following instillation, and corneal epithelial peeling was observed in up to 4/6 eyes between 24 and 72 hours. Effects subsided from all treated eyes by 7 days.

In this study, EXP-31498A is a moderate ocular irritant, and is classified as TOXICITY CATEGORY III for primary eye irritation based on degree of ocular effects which subsided in all treated eyes by 7 days.

This study is classified acceptable (§81-4) and satisfies the guideline requirement for a primary eye irritation study in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

## I. MATERIALS AND METHODS

### A. MATERIALS:

1. Test Material: EXP-31498A  
Description: Clear, light-brown liquid  
Reference #: 218-DAL-95  
Purity: 44.6% (w:w) Acetochlor and 4.2% (w:w) isoxaflutole  
pH: 1.5<sup>1</sup>  
CAS #: 34256-82-1 and 141112-29-0, respectively
2. Vehicle and/or positive control: None employed
3. Test animals: Species: Rabbit  
Strain: Hra: (NZW)SPF  
Age: Young adult (approximately 14 weeks)  
Weight: 2.152-2.391 kg (combined sexes)  
Source: HRP, Inc., Kalamazoo, MI  
Acclimation period: ≥7 Days  
Diet: Purina Laboratory Rabbit Diet HF (#5326), unspecified measured amount/animal/day  
Water: Tap water, ad libitum

### B. STUDY DESIGN and METHODS:

1. In-life dates: October 17-24, 1996
2. Animal assignment and treatment: Approximately 5 minutes prior to treatment, both eyes of each animal were anesthetized with 0.5% proparacaine hydrochloride. A 0.1-mL aliquot of EXP-31498A was then instilled into the conjunctival sac of the right eye of six young adult rabbits (five male and one female). The upper and lower lids were held

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<sup>1</sup>Typically, guidelines §81-4 and 81-5 may be waived for substances having a pH of ≤2 or ≥11.5.

together for approximately 1 second before releasing to prevent loss of the material. The treated eyes were not rinsed, and the left eye of each animal served as an untreated control. The animals were observed for ocular irritation at 1, 24, 48, 72, and 96 hours and 7 days following instillation; eye irritation was scored by the Draize scheme. Beginning at the 24-hour observation interval, fluorescein dye was used to confirm the presence or absence of corneal ulceration.

## II. RESULTS AND DISCUSSION:

- A. Clinical observations: Based on the average irritation score of 34.8, ocular effects were greatest in the treated eyes 1 hour following instillation. At 1 hour, irritation included scattered or diffuse corneal opacity (score of 1) affecting from 25 to 100% of the total area (scores of 2-4), circumcorneal injection of the iris (score of 1), moderate conjunctival redness (score of 2), slight to moderate conjunctival chemosis (scores of 2-3), and severe clear conjunctival discharge (score of 3) in 6/6 treated eyes. At 96 hours, scattered or diffuse corneal opacity (score of 1) affecting up to 25% of the total area (score of 1) persisted in 1/6 eyes, circumcorneal injection of the iris (score of 1) persisted in 2/6 eyes, slight to moderate conjunctival redness (scores of 1-2) persisted in 5/6 eyes, and very slight conjunctival chemosis (score of 1) persisted in 5/6 eyes. Blanching was also observed in up to 6/6 treated eyes between 1 and 48 hours following instillation, and corneal epithelial peeling was observed in up to 4/6 eyes between 24 and 72 hours. Effects subsided from all treated eyes by 7 days. In this study, EXP-31498A is a moderate ocular irritant.
- B. Deficiencies: Aside from ocular effects, individual observations for the entire day of dosing and daily thereafter were not conducted; however, this deficiency has no effect on the results of this study and is considered minor.

EPA Reviewer: Masih Hashim  
Review Section: Technical Review Branch (7505C)

MLH

## DATA EVALUATION RECORD

STUDY TYPE: Primary Dermal Irritation - Rabbit

OPPTS Number: 870.2500

OPP Guideline Number: §81-5

DP BARCODE: D235987

SUBMISSION CODE: S523853

P.C. CODE: 121601 and 123000

TOX. CHEM. NO.:

EPA REG. NO.: 264-LTE

TEST MATERIAL (PURITY): EXP-31498A [44.6% (w:w) acetochlor and 4.2% (w:w) isoxaflutole]

SYNONYMS: Balance Pro Herbicide; RPA201772 (isoxaflutole); 4-(2-methanesulfonyl-4-trifluoromethylbenzoyl)-5-cyclopropyl isoxazole (isoxaflutole); 2-chloro-N-(ethoxymethyl)-N-(2-ethyl-6-methylphenyl) acetamide (acetochlor)

CITATION: Glaza, S. (1997) Primary dermal irritation study of EXP-31498A in rabbits. Corning Hazleton Inc., Madison, WI. Laboratory Project Identification CHW 60904133. January 30, 1997. MRID 44236206. Unpublished.

SPONSOR: Rhone-Poulenc Ag Company, P.O. Box 12014, 2 T.W. Alexander Drive, Research Triangle Park, NC.

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 44236206), three young adult New Zealand White rabbits/sex were dermally exposed to 0.5 mL of EXP-31498A [44.6% (w:w) acetochlor and 4.2% (w:w) isoxaflutole] for 4 hours. The test material was applied as received to a single intact 6.25-cm<sup>2</sup> site/animal. Animals were observed for dermal irritation for up to 21 days following application, and irritation was scored by the Draize scale.

Dermal effects were most severe 72 to 96 hours following application (average score of 6.3) and included well-defined to severe erythema (mean of 3.33) and slight to severe edema (mean of 3.00) at 6/6 sites. At 21 days, very slight erythema persisted at 1/6 sites and very slight to slight edema persisted at 3/6 sites. Additional dermal effects observed included blanching at up to 6/6 sites between 4 and 96 hours, subcutaneous hemorrhaging at up to 4/6 sites between 24 and 96 hours, possible necrotic areas at up to 3/6 sites between 48 and 96 hours, denuded areas at 3/6 sites at 7 days, desquamation at 6/6 sites at 7 days, and possible scar tissue at up to 2/6 sites between 14 and 21 days. The primary dermal irritation index was 6.0.

In this study, EXP-31498A is a severe to corrosive dermal

irritant, and is classified as TOXICITY CATEGORY I for primary dermal irritation based on the degree of effects observed at 72 hours in conjunction with the possible scar tissue observed at 2/6 sites between 14 and 21 days.

This study is classified acceptable (§81-5) and satisfies the guideline requirement for a primary dermal irritation study in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

## I. MATERIALS AND METHODS

### A. MATERIALS:

1. Test Material: EXP-31498A  
Description: Clear, light-brown liquid  
Reference #: 218-DAL-95  
Purity: 44.6% (w:w) Acetochlor and 4.2% (w:w) isoxaflutole  
pH: 1.5<sup>1</sup>  
CAS #: 34256-82-1 and 141112-29-0, respectively
2. Vehicle and/or positive control: None employed
3. Test animals: Species: Rabbit  
Strain: Hra: (NZW)SPF  
Age: Young adult (approximately 14 to 18 weeks)  
Weight: 2.216-2.461 kg (combined sexes)  
Source: HRP, Inc., Kalamazoo, MI  
Acclimation period: >7 Days  
Diet: Purina Laboratory Rabbit Diet HF (#5326), unspecified amount/animal/day  
Water: Tap water, ad libitum

### B. STUDY DESIGN and METHODS:

1. In-life dates: October 15-November 7, 1996
2. Animal assignment and treatment: Fur from the back and/or flank areas of three young adult animals/sex was clipped 1 day prior to dermal administration with 0.5 mL of EXP-31498A. The test material was applied as received to a single intact site/animal. The treated area was covered with an 8-ply 6.25-cm<sup>2</sup>

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<sup>1</sup>Typically, guidelines §81-4 and 81-5 may be waived for substances having a pH of ≤2 or ≥11.5.

gauze patch secured with non-irritating paper tape, then the entire trunk of each animal was loosely wrapped with Saran Wrap and secured with Elastoplast tape. The coverings were removed 4 hours following application, and the test sites were gently washed with tap water and disposable towels. The rabbits were observed for dermal irritation at 4 (30 minutes following patch removal), 24, 48, 72 and 96 hours and 7, 14, and 21 days following application. Erythema and edema were scored separately using the Draize scale.

## II. RESULTS AND DISCUSSION:

- A. Clinical observations: Based on the average irritation score of 6.3, dermal effects were most severe 72 to 96 hours following application. At 72 and 96 hours, well-defined to severe erythema (scores of 2-4; mean of 3.33) and slight to severe edema (scores of 2-4; mean of 3.00) were observed at 6/6 sites. Irritation gradually lessened during the 21-day study; however, at 21 days, very slight erythema (score of 1) persisted at 1/6 sites and very slight to slight edema (scores of 1-2) persisted at 3/6 sites. Additional dermal effects observed included blanching at up to 6/6 sites between 4 and 96 hours, subcutaneous hemorrhaging at up to 4/6 sites between 24 and 96 hours, possible necrotic areas at up to 3/6 sites between 48 and 96 hours, denuded areas at 3/6 sites at 7 days, desquamation at 6/6 sites at 7 days, and possible scar tissue at up to 2/6 sites between 14 and 21 days. The primary dermal irritation index (0- to 72-hour) was 6.0. In this study, EXP-31498A is a severe to corrosive dermal irritant.
- B. Deficiencies: Aside from dermal effects, individual observations for the entire day of dosing and daily thereafter were not conducted; however, this deficiency has no effect on the results of this study and is considered minor.